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Incidence and Risk Factors for Hepatitis C among Injection Drug Users in Baltimore, Maryland

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Between 1988 and 1996, the incidence of and risk factors for hepatitis C virus (HCV) infection were studied in a cohort of injection drug users in Baltimore, Maryland. By second-generation antibody testing of stored serum samples, 142 participants were found to be susceptible to HCV at the time they entered the study. After a median follow-up of 6.5 years, 43 participants (30.3%) developed antibodies to HCV (anti-HCV). The overall incidence was 6.4 cases per 100 person-years, but a substantial decline in the annual incidence rate was observed after the first 2 years (1988 to 1990, 13.4/100 person-years; 1991 to 1996, 2.3/100 person-years [$P = 0.0001$ for trend]). Participants who acknowledged active drug use, especially those who acknowledged frequent use and sharing of drug paraphernalia, were at increased risk of HCV infection. However, high-risk sexual practices were not associated with HCV seroconversion. Efforts to reduce HCV infection must be focused on curbing drug use and especially on the sharing of needles and drug paraphernalia.

Hepatitis C virus (HCV) is the major cause of non-A, non-B hepatitis worldwide and the leading cause of chronic viral hepatitis in the United States (3). It is currently estimated that 3.9 million people in this country are infected (1). Chronic HCV infection is strongly associated with cirrhosis, liver cancer, and end-stage liver disease requiring transplantation (8, 14, 22, 24). Since existing therapies are successful in fewer than one-third of cases, and no HCV vaccine is available, efforts to reduce HCV transmission are crucial to reducing the impact of this disease.

In the United States, injection drug use is the principal route of HCV transmission, accounting for up to 42% of acute cases (2, 3). Most studies of injection drug users (IDUs) have demonstrated HCV seroprevalence rates from 60 to 90%. In these cross-sectional studies, HCV infection generally correlates with drug use practices as opposed to sexual behaviors or demographic factors (6, 9, 23, 25). However, such associations could be missed, since transmission may have occurred years before behaviors were evaluated. We are aware of no prospective studies of hepatitis C among IDUs in the United States. Thus, we conducted a historical prospective investigation in a well-characterized cohort of IDUs who have been monitored in Baltimore, Md., since 1988.

MATERIALS AND METHODS

Participants. Between 1988 and 1989, 2,921 IDUs from the Baltimore area were enrolled in the AIDS Link to the Intravenous Experience (ALIVE) study, a longitudinal investigation of the natural history of human immunodeficiency virus (HIV) infection (26). Participants were at least 18 years of age and free of AIDS and acknowledged a history of injection drug use in the previous 10 years. At the initial visit, a serum sample was collected and an interview about demographic data and drug injection practices was conducted. Participants, irrespective of HIV status, were then monitored at 6-month intervals by serum collection and interview.

For this investigation, a cohort of individuals susceptible to HCV was constructed retrospectively by testing stored serum samples. Participants with serum samples available from their first (enrollment) visit and from at least 1 year after enrollment were evaluated for the presence of antibodies to HCV (anti-HCV). Those participants who were negative for anti-HCV at enrollment were tested again with the most recent serum sample available as of May 1996. Participants who were found to be seropositive for hepatitis C at their latest visit were then tested at all available intermediate time points necessary to identify the time of seroconversion. Anti-HCV seroconversions were confirmed by testing for HCV RNA at serial visits and, if the results were negative, by supplemental antibody testing (immunoblot assay).

Laboratory methods. All serum samples were stored at −70°C. All testing for antibody to HCV was performed in our laboratory with the second-generation HCV 2.0 enzyme immunoassay (Ortho Diagnostic Systems, Raritan, N.J.) according to the manufacturer's specifications. In addition, all tests yielding negative results were repeated at least once. HCV RNA was detected with a commercially available quantitative reverse transcriptase PCR assay (Amplicor HCV Monitor Test kit; Roche Diagnostic Systems, Branchburg, N.J.). Serum samples from HCV antibody-positive and HCV RNA-negative participants were also tested with the RIBA HCV 2.0 strip immunoblot assay (Chiron Corporation, Emeryville, Calif.).

Statistical analysis. Incidence rates were calculated for each 12-month period after enrollment by person-time methods (5). The date of HCV seroconversion was estimated as the midpoint between the last negative and the first positive visit. Incidence rates were calculated as the number of seroconversions divided by the person-years at risk for each year postenrollment. In addition, the cumulative incidence of infection, defined as 1 − the survival function, was derived from the Kaplan-Meier procedure (17). Poisson regression methods were used to investigate the linear trend in the natural log of the HCV incidence rate over time since enrollment (5). The Wald test was used to determine the significance of a time trend.

To investigate risk factors for HCV seroconversion, a matched case-control study of seroconverters and seronegative individuals was nested within the historical prospective study of initially HCV-seronegative participants. For each case of HCV seroconversion, four HCV-seronegative IDUs were matched for semester of entry into the study and duration of follow-up. In addition, controls were required to have a visit within 90 days of the first seropositive visit of the case. The control group was made up of individuals found to be HCV seronegative throughout this study. Seroconverters for HCV were also eligible to serve as controls until 12 months prior to their estimated seroconversion dates. Multiple visits from one participant could serve as control visits; hence, the number of control visits was greater than the number of seronegative individuals. Risk-behavior information (which refers to drug use and sexual practices during the preceding 6 months) obtained at the matched visits was used in the analysis of HCV seroconversion via conditional logistic regression techniques.

RESULTS

Participants. A total of 1,593 participants enrolled in the study in 1988 or 1989 had serum available for HCV testing from a visit at least 1 year after their first visit. At enrollment, 142 (8.9%) of the 1,593 participants were anti-HCV negative

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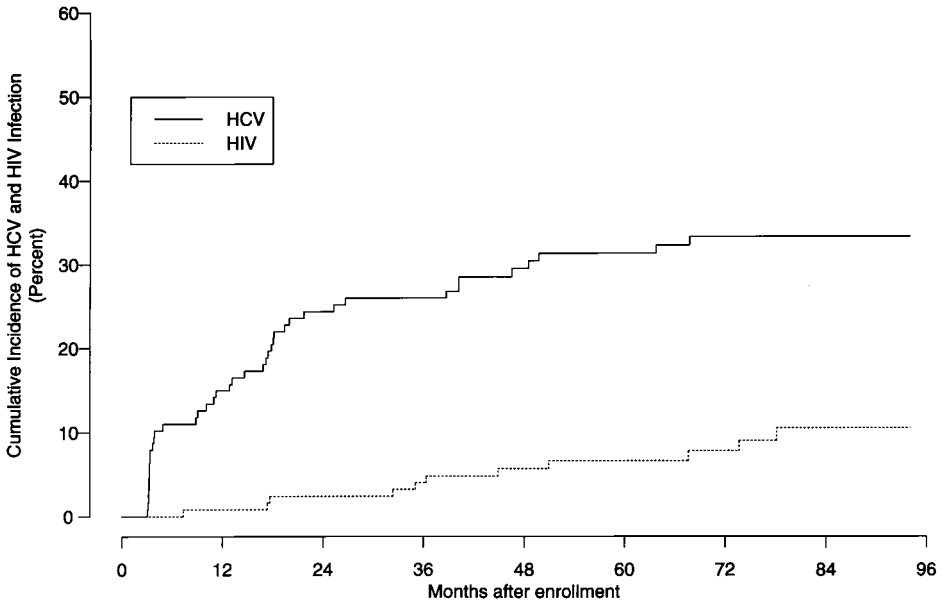

HCV	SC	19	12	2	4	2	2	0	0
	PYR	118.2	103.2	95.0	84.7	74.7	67.8	55.9	14.9
	RATE	16.1	11.6	2.1	4.7	2.7	2.9	0	0
HIV	SC	1	2	4	2	1	1	2	0
	PYR	128.5	126.8	123.4	109.4	99.8	86.1	59.8	14.7
	RATE	0.8	1.6	3.2	1.8	1.0	1.2	3.3	0

FIG. 1. Cumulative incidence of HCV and HIV infection among 129 injection drug users who were susceptible to both infections at enrollment in the study. Number of seroconversions (SC), person-years of observation (PYR), and rate of seroconversion per 100 person-years (RATE) are shown below the *x* axis for each 12-month interval after enrollment. Over the 8-year follow-up, there were a total of 41 HCV and 13 HIV seroconversions in this group.

by the second-generation assay. The sociodemographic and drug use correlates according to their HCV status at enrollment were previously described for most participants (23). In brief, compared to anti-HCV-positive participants, anti-HCV-negative participants were younger and less likely to be black and had used drugs for a shorter period of time and less frequently. Anti-HCV-negative participants were also less likely to have shared needles in any setting and had a lower prevalence of HIV and HBV infections based on serologic testing.

Incidence rates. During a median follow-up of 6.5 years (range, 2.4 to 7.8 years), 47 of 142 participants became HCV seropositive. HCV RNA was detected in 42 participants, and one additional seroconversion was confirmed by immunoblot assay, resulting in a total of 43 confirmed HCV seroconverters (30.3% of 142).

The overall incidence of HCV infection over 8 years was 6.4 cases per 100 person-years. However, a significant downward trend in the incidence rate was detected every year after enrollment (linear trend test, $P = 0.0001$). During the first 2 years, the rate averaged 13.4 cases per 100 person-years. In contrast, there were only 2.3 cases per 100 person-years in the last 6 years, during which there were still 430 person-years of follow-up. The median time to seroconversion was 1.1 years (range, 0.3 to 5.7 years).

Of the 142 initially anti-HCV-negative participants, 13 (9.2%) were infected with HIV at enrollment. No difference was detected in the overall incidence of HCV infection among HIV-positive and -negative participants (3.3 versus 6.7/100 person-years, respectively; $P = 0.33$). Among the subgroup of 129 participants susceptible to both HCV and HIV at enrollment, a total of 41 HCV seroconversions and 13 HIV seroconversions were observed over the 8 years of follow-up, resulting in an overall incidence rate of 6.7 per 100 person-years for HCV and 1.7 per 100 person-years for HIV (Fig. 1). The marked difference in cumulative incidence is largely due to the high rate of HCV seroconversion in the first 2 years after enrollment. While the annual HCV incidence rate generally declined after this point, the incidence of HIV varied relatively little over time.

Of the 41 new cases of HCV infection that were identified in the group initially susceptible to both viruses, 11 also acquired HIV, and HCV was acquired before HIV in 10 of the 11 cases of dual infection. Thus, only two individuals from this group acquired HIV alone.

Risk factors. The risk of HCV infection did not differ according to age, gender, level of education, employment status, or duration of drug use at enrollment. Also, there was no association between the risk of HCV infection and homelessness, income in the year before enrollment, or incarceration in the 10 years before enrollment ($P > 0.10$).

HCV seroconverters were more likely to have reported recent injection drug use (i.e., in the previous 6 months), frequent drug use (more than once per day), sharing needles, attending a "shooting gallery," sharing cookers (small containers used to prepare drug solutions), and not always using their own needles. In bivariate analyses of seroconversion, the highest risk for HCV infection was found among frequent drug

TABLE 1. Conditional logistic regression of injection drug use practices associated with HCV seroconversion

Variable[a]	*n* (%)		Odds ratio (95% confidence interval)
	Seroconverters (*n* = 43)	Seronegatives[b] (*n* = 172)	
Recent drug use			
No	12 (27.9)	99 (57.6)	1.0
Yes	31 (72.1)	73 (42.4)	3.8 (1.7–8.4)
Frequency of drug use			
None	12 (27.9)	99 (57.6)	1.0
Less than once daily	14 (32.6)	45 (26.2)	2.9 (1.2–7.1)
At least once daily	17 (39.5)	28 (16.3)	5.1 (2.1–12.9)
Sharing needles			
No drug use	12 (27.9)	99 (57.6)	1.0
Use without sharing	15 (34.9)	46 (26.7)	3.0 (1.2–7.1)
Use with sharing	16 (37.2)	27 (15.7)	5.7 (2.2–14.4)
Attendance at shooting gallery			
No drug use	12 (27.9)	99 (57.6)	1.0
Use, not at gallery	23 (54.8)	60 (34.9)	3.4 (1.5–7.7)
Use, at gallery	7 (16.7)	13 (7.6)	5.7 (1.7–19.8)
Sharing cookers			
No drug use	12 (27.9)	99 (57.6)	1.0
Use, without cookers	10 (23.3)	31 (18.0)	2.9 (1.1–7.5)
Use, with cookers	21 (48.8)	42 (24.4)	4.7 (2.0–11.1)
Using own needles			
No drug use	12 (27.9)	99 (57.6)	1.0
Always use own needles	15 (34.9)	49 (28.5)	2.8 (1.2–6.6)
Do not always use own needles	15 (34.9)	22 (12.8)	6.2 (2.4–16.4)
Frequency/needle sharing			
No drug use	12 (27.9)	99 (57.6)	1.0
Less than once daily/no sharing	10 (23.3)	31 (18.0)	3.0 (1.1–7.8)
Less than once daily/sharing	4 (9.3)	14 (8.1)	2.8 (0.7–10.8)
At least once daily/no sharing	5 (11.6)	15 (8.7)	2.8 (0.9–9.2)
At least once daily/sharing	12 (27.9)	13 (7.6)	8.1 (2.8–23.0)
Frequency/gallery use			
No drug use	12 (27.9)	99 (57.6)	1.0
Less than once daily/no gallery use	12 (27.9)	37 (21.5)	2.8 (1.1–7.0)
Less than once daily/gallery use	1 (2.3)	8 (4.7)	1.3 (0.1–12.1)
At least once daily/no gallery use	11 (25.6)	23 (13.4)	3.6 (1.4–9.1)
At least once daily/gallery use	6 (14.0)	5 (2.9)	10.8 (2.6–45.3)

[a] Variables are drug use practices reported in the 6 months prior to the matched visit.

[b] Four nonconverter visits were matched to each case at the visit when seroconversion was first observed.

users who reported sharing needles or attending a shooting gallery (Table 1). Sexual orientation, number of sex partners, trading sex for money, and history of sexually transmitted disease were not significantly associated with HCV infection ($P > 0.10$). Adjusting for age at enrollment did not alter the relative risk estimates for any drug use or sexual practice variables.

DISCUSSION

This investigation confirms, as has been suggested in cross-sectional studies, that IDUs have a high risk of HCV infection that is principally acquired through illicit drug use practices. The incidence of HCV infection (6.4 cases per 100 person-years) found in this study was comparable to what has been found among European IDUs (7, 10, 20, 25). However, in this study a marked decrease in the incidence of HCV infection was observed after the first 2 years. This decrease coincided with a nationwide decrease in the number of HCV infections related to drug use that were reported to the Centers for Disease Control and Prevention (4). However, there is no evidence in Baltimore of community-wide reductions in high-risk drug use behaviors. In fact, a high incidence of HCV (18%) was recently observed among young IDUs from Baltimore (11).

It is more likely that the marked decrease in the incidence of HCV in this cohort reflects a saturation of the at-risk population. By 1991, when the incidence of HCV decreased, more than 93% of the active participants in this ALIVE cohort were already infected. Many of the remaining participants who were not infected with HCV had stopped using illicit drugs, eliminating their principal risk for infection. A small number continued injecting (some shared needles) but remained uninfected with HCV. More studies are needed to assess biological factors and other factors that may explain this rare outcome. A similar saturation of the at-risk population probably also explains the decrease in the incidence of HBV previously observed in this cohort (16). In contrast, the incidence of HIV has remained stable in this ALIVE cohort, as more than 50% of the members remain susceptible (19).

Several factors may contribute to the high incidence of HCV relative to that of other blood-borne infections among IDUs. The more frequent persistence of HCV compared to that of HBV is important. More than 90% of adults become noninfectious after HBV infection, limiting the reservoir for transmission (21). In contrast, over 80% of HCV infections persist (1). Thus, among IDUs there is a large reservoir of HCV from which new injection drug users are infected. Persistence is even higher for HIV infection than for HCV infection. However, the prevalence of HIV is less than that of HCV among drug-using populations, and HIV is less transmissible through parenteral exposure. Approximately 0.3% of persons exposed accidentally to HIV by being stuck with a needle become infected (12), while for HCV the frequency is at least 10-fold higher (15, 18).

This prospective investigation showed evidence only of injection drug use-related HCV transmission. Given the associated morbidity and mortality and the lack of an HCV vaccine, efforts to prevent HCV infection must be focused on reducing injection drug use and practices involving the sharing of drug use equipment. Strategies such as needle exchange programs may be effective in this way, as has been recently demonstrated (13). However, more studies are urgently needed to confirm this finding and to develop and apply other methods of curtailing the transmission of infectious diseases by illicit drug use.

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